The New Faces of Cutaneous Lymphoma

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N. Pimpinelli, M. Santucci**, B. Giannotti**

Departments of* Dermatology II and ** Human Anatomy and Histology, University of Florence, Italy

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Abstract. Cutaneous lymphomas are well known diseases which present and arise in the skin, in the absence of any detectable extracutaneous lesion. In this paper, the authors review their studies and those in the literature, outlining the continuously increasing data concerning the immunophenotypical and genotypical features of lymphomas.

What are the "new faces" of cutaneous lymphoma (CL) ? Simply, those derived from new and powerful tools for the characterization of lymphoid cells and from their application to carefully done clinico-pathologic studies. Indeed, the present concept of CL has been deeply influenced by the continuously increasing amount of available data concerning its immunophenotypic and genotypic features, and their correlation with clinical and histologic patterns. Furthermore, the definition of new, basic standpoints in the immunologic properties of the skin — with the consequent development of the concept of skin-associated lymphoid tissue (SALT)[1] and skin immune system (SIS)[2] — has created the biological basis for the hypothesis of CL as a neoplasm possibly related to SALT/SIS.

In our view, one of the most important drawbacks of the research in this field is that of dealing with the definition of CL and its clinical implications. It is now recognized that the involvement of the skin secondary to nodal lymphomas has nothing to do with CL. This latter term should only concern lymphomas which present (and possibly arise) in the skin, in the absence of any detectable extracutaneous lesion, despite careful and complete staging procedures. The concept of CL has an immediate clinical consequence: these neoplasms can be treated, as a rule, less aggressively than systemic lymphomas, with proper modalities and protocols mainly affecting the skin. An aggressive treatment with systemic chemotherapy has not been proven as more effective than a softer one with other procedures (specified below) in improving the overall prognosis. Therefore, it should be used only in case of widespread dissemination of nodular and/or tumorous lesions on the skin and, of course, when extracutaneous spread does occur.

The diagnosis of CL, its classificacion, and its differentiation from reactive lymphoproliferative disorders (pseudolymphomas) are now supported by immunophenotyping and genotyping. In fact, the demonstration of clonality is now accepted by most people as the key criterium for the diagnosis of CL and its differentiation from pseudolymphoma. The immunohistochemical finding of immunoglobulin (Ig) light chain monoclonal restriction by neoplastic B-cells and/or the DNA analysis demonstration of a monoclonal rearrangement of Ig heavy chain or

T-cell receptor genes have to be considered the most reliable criteria for the diagnosis of lymphoma, especially when the histologic features are not conclusive.

According to the histoimmunologic (and genotypic) features, CL can be distinguished in two main groups with quite different clinical behaviour and prognosis. Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group, in which different clinico-pathologic subtypes can be recognized; this classification has clinical and therapeutic relevance. In fact, the natural history of CTCL may be very different according to the clinico-pathologic and immunophenotypic features of the disease at presentation. On this basis, we can now recognize at least three main subgroups: *mycosis fungoides* (MF), *CD30+ large cell CTCL non-MF*, and *CD30- large cell CTCL non-MF*. Mycosis fungoides is classically defined by its prolonged and typical course: an early patch stage, in which the diagnosis may be very difficult[3], even with the aid of additional investigations (genotyping); a plaque stage, characterized by the prototypical band-like infiltration of cerebriform cells; and a tumour stage, characterized by a diffuse infiltration of large blast cells and associated with a poor prognosis. Most dermatologists know that MF can be (and should be) successfully treated with non-aggressive procedures in its patch/plaque stage. Photochemotherapy, topical chemotherapy or total skin electron beam irradiation can be chosen in this, sometimes, very prolonged phase, according to the number, diffusion and thickness of the skin lesions. In the tumour stage, or in the presence of a specific lymph nodal involvement, chemotherapy (COP or CHOP courses) is indicated[4], even though it generally gives poor results. CD30-large cell CTCL non-MF are characterized by presentation with single or - more frequently - multiple skin nodules or tumorus, rapid course, and poor prognosis, despite aggressive treatment[5]. CD30+ CTCL non-MF have been almost recently recognized as a clinico-pathologic entity. They are currently defined as primary cutaneous CD30+ large cell lymphomas[5,6], irrespective of their morphologic classification (anaplastic or non-anaplastic, according to the definition of the updated Kiel classification[7]). They are characterized by presentation with solitary or localized skin lesions, which possibly show spontaneous remission (partial to complete) (Fig. 1); good and rapid respon-

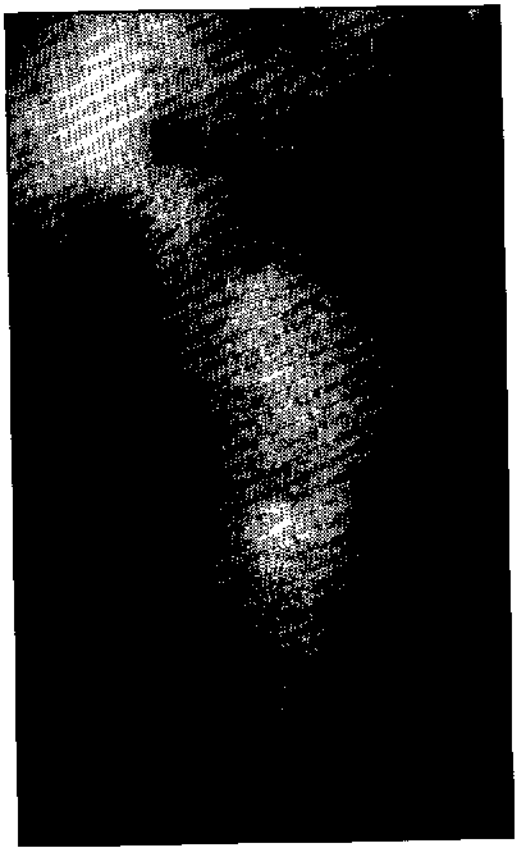

Fig. 1 - CD30+ large cell CTCL. Ulcerated, crusted plaque and hyperpigmented, atrophic patches (resulting from the evolution of skin lesions: infiltration, ulceration, crusting and self healing, with variable degrees of atrophy and scarring) on the left thigh.

se to local radiotherapy (orthovolt or megavolt); and favorable prognosis, despite frequent cutaneous relapses. These CD30+ large cell CTCL are considered by most experts as part of a spectrum of cutaneous lymphoproliferative disorders, all characterized by the presence of variable numbers of large CD30+ atypical cells spontaneous regression of skin lesions, and benign evolution. This spectrum includes CD30+ large cell CTCL, lymphomatoid papulosis [9] (Fig.2) and regressing

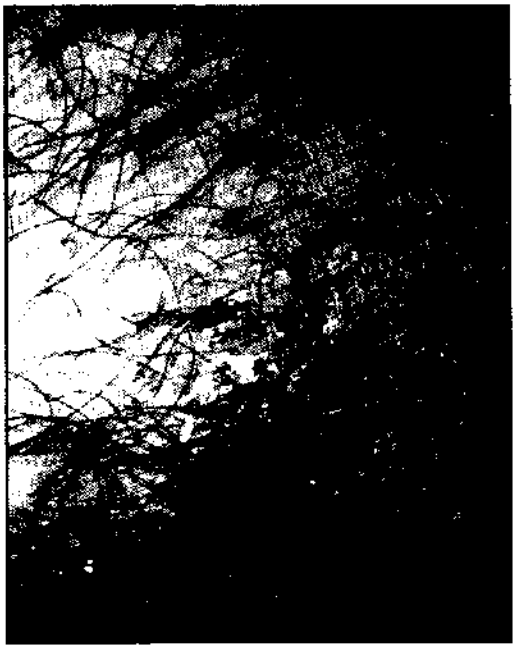

Fig. 2 - Spectrum of CD30+ cutaneous lymphoproliferative disorders: lymphomatoid papulosis, a continuing, self-healing eruption, clinically benign, histologically malignant. Small, crusted nodule of the right lower leg. The evolution of skin lesions is typical: eruption of papulo-nodular lesions, ulceration, crusting and self-healing without scarring.

atypical histiocytosis [10] (Fig. 3). The classification of these latter two clinico-pathologic entities as low-grade malignancy CTCL is currently a matter of debate [11,12]. CD30 antigen expression by proliferating T-cells in the skin, therefore, seems to

Fig. 3 - Spectrum of CD30+ cutaneous lymphoproliferative disorders: regressing atypical histiocytosis. Large plaque of the upper, anterior part of the right thigh, showing the signs of its natural history: advancing, infiltrated border; ulceration; pigmentation and scarring.

have an important biologic implication. Nevertheless, it is noteworthy to emphasize that large cell CTCL, either CD30+ or CD30-, always have a bad prognosis if they represent the final evolution (tumour stage) of MF.

On the other hand, cutaneous B-cell lymphomas (CBCL) have — according to the data reported in the more detailed and consistent papers [13-16] — a quite homogeneous clinical behaviuor, with very low tendency to extracutaneous spread and excellent prognosis. Most patients present with nodules and/or tumours, more often typically surrounded by small, slightly infiltrated plaques and/or figurate erythematous lesions (Fig.4); the latter, may have preceded of months to years the development of rapidly growing skin tumours. Skin lesi-

Fig. 4 - CBCL. Typical features at presentation: large tumorous lesion, surrounded by slightly infiltrated plaques, on the back of a male patient. These latter lesions had preceded the rapid growth of the tumour for more than 6 years.

ons usually have a loco-regional extension, widespread lesions at presentation being the least frequent occurrence [16]. Orthovolt radiotherapy is highly effective and subjectively well-accepted, and has to be considered the treatment of choice, either at presentation or on relapse. Chemotherapy is indicated in only a minority of patients, i.e. those with widespread cutaneous lesions and those who developed extracutaneous spread of the disease. The response to the above treatments is definitely good, with a very high rate of complete remissions [16]. In selected cases, the surgical excision of isolated nodular lesions may be sufficient. CBCL show, despite relatively frequent cutaneous relapses, a low tendency to the extracutaneous spread and a very low mortality rate [16]. According to our experience, no correlation does exist between clinical features at presentation (type of lesions, single vs. multiple, or localized vs. widespread lesions) and overall prognosis (extracutaneous spread and/or death of the patient). As in CTCL, the presence of skin lesions only should be referred to as stage I [17]. Differently from CTCL, however, the identification of further clinical subgroups does not seem to have any prognostic relevance in CBCL.

The main criteria to be met for the diagnosis of CBCL are: 1- *a*bsence of any detectable extracutaneous lesion (despite extensive and careful staging procedures, including chest X-rays, abdominal US and/or CT scan and bone marrow biopsy) for at least 6 months from diagnosis; 2 - expression of B--cell restricted antigens (CD19, CD20, CD22) by neoplastic cells; 3 - light chain monoclonal restriction of sIg in neoplastic cells. This latter point is essential for the

differentiation of CBCL from B-cell pseudolymphomas of the skin[18].

The accepted classifications and formulations of non-Hodgkin's lymphomas are difficult to apply — and are not working — in CBCL, as well as in other extranodal lymphomas, e.g., lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma)[19]. Therefore, these lymphomas should be considered as a distinct entity[7]. The spectrum of histologic (cytologic and architectural) and immunohistologic patterns we found in CBCL is largely related to the age and growth rates of skin lesions[16]. This spectrum ranges from the sometimes inconspicuous "top heavy" infiltrate of intermediate-sized neoplastic B-cells and many reactive T-cells observed in early lesions (" low grade" malignancy picture, classically considered typical of cutaneous pseudolymphomas) to the uniformly heavy dermal infiltrate of large neoplastic B-cells ("high grade" malignancy picture) characteristic of late, rapidly growing lesions. This variability has no correlation with either the clinical presentation and course or, more importantly, to the prognosis of CBCL, which is overall good. Therefore, at present, the identification of morphologic subgroups has no clinical, therapeutic and/or prognostic relevance. The above data, along with the uniform immunophenotypic (Leu8+, CD5-, CD10-) and genotypical features of neoplastic B-cells (lack of bc1-2 gene rearrangement)[20,21], strongly support the single nature of CBCL[16]. The striking similarities between CBCL and MALT lymphoma[6,19,22] (preferentially loco-regional extension; non-aggressive clinical behaviour; good response to local treatments; histologic finding of so-called centrocyte-like cells, reactive lymphoid follicles and lymphoepithelial lesions; CD5-, CD10- immunologic phenotype of neoplastic B-cells; and lack of bc1-2 gene rearrangement) suggest the interpretation of CBCL as the cutaneous counterpart of MALT lymphoma, i.e., SALT-related B-cell lyphoma[22,23]. The recent report of CBCL as the first manifestation of AIDS, seems to give support to this hypothesis[24].

In conclusion, are there faces of CL which remain obscure? Yes, of course. The possible viral aetiology of CTCL, at least in some of them, has been deeply investigated for several years, but conflicting results and interpretations have originated[25]. The early diagnosis of CTCL remains the most formidable challenge for dermatopathologists, and histology should still be considered the "golden standard" tool for diagnosis. The cardinal features of early CTCL are represented by 1) the epidermal infiltration of medium-to large-sized cerebriform lymphocytes, predominantly as single cells, in a somewhat linear configuration; and 2) the presence of discrete collections of medium-to large-sized cerebriform lymphoid cells in the dermis[3]. The treatment of CTCL continues from being a great problem, and long-term effective, "curative" modalities are really far from being established. In this respect, a promising way seems to be the use of immunomodulation, alone or associated with traditional treatment modalities. Many clinical trials with α-2 recombinant interferon, alone or in association with either PUVA and/or oral retinoids or systemic chemotherapy, have been performed. The extreme variability of schedules and doses on one hand, and of patient selection on the other, does not allow to raise conclusions at the moment[26]. Extracorporeal photophoresis is suggested by some selected groups as extremely promising and effective[27]. Other treatment modalities (monoclonal antibodies, interleukin-2), finally, are definitely experimental.

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REFERENCES

1. Streilein, J.W.: Skin-Associated Lymphoid Tissues (SALT): Origins and Functions. *J. Invest. Dermatol.*, 80: 12s-16s, 1983.
2. Bos, J.D.; Kapsenberg, M.L.: The Skin Immune System (SIS). Its Cellular Constituents and Their Interactions. *Immunol. Today*, 7: 235-240, 1986.
3. Santucci, M.: Cutaneous T-Cell Lymphoma: Clues to Diagnosis in Early Lesions. *In: Basic Mechanisms of Physiologic and Aberrant Lymphoproliferation in the Skin.* Van Vloten, W.A.; Lambert, W.C.; Giannotti, B. Eds. NATO Advanced Research Workshops, Plenum Press. New York (in press).
4. Zachariae, H.: Treatment of Advanced Stages of Cutaneous T-Cell Lymphoma. *In: Dermatology in Europe*, pp. 234-236. Panconesi, E. Ed. Blackwell Scientific Publications, Oxford. 1991.
5. Beljaards, R.C.; Meijer, C.J.L.M.; Scheffer, E. et al. Prognostic Significance of CD30 (Ki-l/Ber-H2) Expression in Primary Cutaneous Large-Cell Lymphomas of T-Cell Origin. A Clinicopathologic and Immunohistochemical Study of 20 Patients. *Am. J. Pathol., 135:* 1169-1178, 1989.
6. Willemze, R.; Beljaards, R.C.; Kaudewitz, P., et al.: Primary Cutaneous CD30-Positive Large Cell Lymphoma: Definition of a New Type of Cutaneous Lymphoma with Favorable Prognosis. *In: Basic Mechanisms of Physiologic and Aberrant Lymphoproliferation in the Skin.* Van Vloten, W.A.; Lambert, W.C.; Giannotti, B. Eds. NATO Advanced Research Workshops, Plenum Press. New York, (in press).
7. Lennert, K.; Feller, A.C.: *Histopathology of Non-Hodgkin's Lymphomas (Based on the Updated Kiel Classification).* 2nd ed., Springer-Verlag. Berlin, 1992.
8. Kadin, M.: The Spectrum of Ki-l+ Cutaneous Lymphomas. *In: Cutaneous Lymphoma, Current Problems in Dermatology"* , vol. 19, pp. 132-143.Van Vloten, W.A.; Willemze, R.; Lange Vejlsgaard, G.; Thomsen, K. Eds. Honigsmann, H. Ed. Karger, Basel, 1990.
9. Macaulay, W.L.: Lymphomatoid Papulosis: A Continuing, Self-Healing Eruption, Clinically Benign, Histologically Malignant. *Arch. Dermatol., 97:* 23-30, 1968.
10. Flynn, K.J.; Denher, L.P.; Kazimiera, J., et al: Regressing Atypical Histiocytosis: A Cutaneous Proliferation of Atypical Neoplastic Histiocytes with Unexpectedly Indolent Biologic Behavior. *Cancer, 49:* 959-970, 1982.
11. Weiss, L.H.; Wood, G.S.; Trela, M.; Warnke, R.A.; Sklar, J.: Clonal T-Cell Populations in Lymphomatoid Papulosis. *N. Engl. J. Med., 315:* 475-479, 1986.
12. Headington, J.T.; Roth, M.S.; Ginsburg, D., et al: T-Cell Receptor Gene Rearrangement in Regressing Atypical Histiocytosis. *Arch. Dermatol., 123:* 1183-1187, 1987.
13. Willemze, R.; Meijer, C.J.L.M.; Sentis, H.J., et al: Primary Cutaneous Large Cell Lymphomas of Follicular Center Cell Origin. *J. Am. Acad. Dermatol., 16:* 518-526, 1987.
14. Berti, E.; Alessi, E.; Caputo, R.; Gianotti, R.; Delia, D.; Vezzoni, P.: Reticulohistiocytoma of the Dorsum. *J. Am. Acad. Dermatol., 19:* 259--272, 1988.
15. Pimpinelli, N.; Santucci, M.; Bosi, A., et al.: Primary Cutaneous Follicular Centre-Cell Lymphoma: A Lymphoproliferative Disease with Favourable Prognosis. *Clin. Exp. Dermatol., 14:* 12-19, 1989.
16. Santucci, M.; Pimpinelli, N.; Arganini, L.: Primary Cutaneous B-Cell Lymphoma: A Unique Type of Low-Grade Lymphoma. Clinicopathologic and Immunologic Study of 83 Cases. *Cancer, 67:* 2311-2326, 1991.
17. Burg, G.; Braun-Falco, O.: Cutaneous Lymphomas, Pseudolymphomas, and Related Disorders. Springer-Verlag, Berlin, 1983.
18. Rijlaarsdam, J.U.; Meijer, C.J.L.M.; Willemze, R.: Differentiation between Llymphoadenosis Benigna Cutis and Primary Cutaneous Follicular Center Cell Lymphomas. A Comparative Clinicopathologic Study of 57 Patients. *Cancer, 65:* 2301-2306, 1990.
19. Isaacson, P.G.; Spencer, J.: Malignant Lymphoma of Mucosa-Associated Lymphoid Tissue. *Histopathol., 11:* 445-462, 1987.
20. Aisenberg, A.C.; Wilkes, B.M.; Jacobson M.: The bc1-2 Gene is Rearranged in Many Diffuse B-Cell Lymphomas. *Blood, 71:* 969-972, 1988.
21. Berti, E.; Gianotti, R.; Alessi, E.; Caputo, R.: Primary Cutaneous Follicular Center Cell

Lymphoma: Immunophenotypical and Immunogenotypical Aspects. *In: Cutaneous Lymphoma, Current Problems in Dermatology*, vol. 19, pp. 196-202. Van Vloten, W.A.; Willemze, R.; Lange Vejlsgaard, G.; Thomsen, K., Eds. Honigsmann, H. Karger, Basel, 1990.

22. Pimpinelli, N.; Santucci, M.; Carli, P., et al.: Primary Cutaneous Follicular Center Cell Lymphoma: Clinical and Histological Aspects. *In: Cutaneous Lymphoma, Current Problems in Dermatology*. Vol. 19, pp. 203-220. Van Vloten, W.A.; Willemze, R.; Lange Vejlsgaard, G.; Thomsen, K. Eds. Honigsmann, H. Karger, Basel, 1990.
23. Santucci, M.; Pimpinelli, N.: Cutaneous B-cell Lymphoma: A SALT-Related Tumor? *In: Basic Mechanisms of Physiologic and Aberrant Lymphoproliferation in the Skin*. Van Vloten, W.A.; Lambert, W.C.; Giannotti, B. Eds. NATO Advanced Research Workshops , Plenum Press. New York, (in press).
24. Vicente, A.; Marti, R.; Estrach, T. et al.: Primary Cutaneous B-Cell Lymphoma as First Manifestation of Acquired Immunodeficiency Syndrome. *Eur. J. Dermatol., 1*: 7-10, 1991.
25. Bernengo, M.G.: Etiology of Cutaneous Lymphomas. *In: Dermatology in Europe*, pp. 226-228. Panconesi, E. Ed.,Blackwell Scientific Publications. Oxford, 1991.
26. Papa, G.; Tura, S.; Mandelli, F. et al.: Is Interferon Alpha in Cutaneous T-Cell Lymphoma a Treatment of Choice ? *Br. J. Haematol., 179 (Suppl.1)*: 48-51, 1991.
27. Edelson, RL.: Immunoregulatory Therapeutic Control of Cutaneous Lymphoma. *In: Basic Mechanisms of Physiologic and Aberrant Lymphoproliferation in the Skin*. Van Vloten, W.A.; Lambert, W.C.; Giannotti, B. Eds. NATO Advanced Research Workshops, Plenum Press. New York, (in press).

Prof. B. Giannotti,
Clinica Dermosifilopatica II
University of Florence
Via della Pergola, 58
I-50121 Florence
(Italy).